

Safety of anti-tumor necrosis factor therapy during pregnancy in patients with inflammatory bowel disease

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Abstract

Treatment of inflammatory bowel disease has sign-

ificantly improved since the introduction of biological agents, such as infliximab, adalimumab, certolizumab pegol, and golimumab. The Food and Drug Administration has classified these factors in category B, which means that they do not demonstrate a fetal risk. However, during pregnancy fetuses are exposed to high anti-tumor necrosis factor (TNF) levels that are measurable in their plasma after birth. Since antibodies can transfer through the placenta at the end of the second and during the third trimesters, it is important to know the safety profile of these drugs, particularly for the fetus, and whether maintaining relapse of the disease compensates for the potential risks of fetal exposure. The limited data available for the anti-TNF drugs to date have not demonstrated any significant adverse outcomes in the pregnant women who continued their therapy from conception to the first trimester of gestation. However, data suggest that anti-TNFs should be discontinued during the third trimester, as they may affect the immunological system of the newborn baby. Each decision should be individualized, based on the distinct characteristics of the patient and her disease. Considering all the above, there is a need for more clinical studies regarding the effect of anti-TNF therapeutic agents on pregnancy outcomes.

Key words: Anti-tumor necrosis factor; Pregnancy; Adverse effects; Crohn's disease; Ulcerative colitis; Inflammatory bowel disease

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Core tip: Modern inflammatory bowel disease treatment includes biological therapy, such as anti-tumor necrosis factor (TNF) agents. There are concerns over the use of anti-TNF agents during pregnancy, although the data available to date are limited. No significant increases in the adverse outcomes of pregnancy have been reported in women who continued their treatment from conception to the first trimester of pregnancy.

Decision making in this case dictates that the mother's benefits of maintaining relapse of the disease through continuation of anti-TNFs exceeds the potential risks of fetal exposure.

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INFLAMMATORY BOWEL DISEASE AND ANTI-TNF THERAPY

Anti-tumor necrosis factor (TNF) agents are an effective therapeutic option in patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD). The highest incidence of IBD is seen between the second and fourth decades of life, which is the most fertile age for women. However, data concerning their safety during pregnancy are scarce.

CD usually affects people between the second and third decades of life, thereby having a negative impact on pregnancy outcomes. Simultaneously, pregnancy itself can negatively affect the outcome of CD^[1]. Approximately 25% of women with IBD can achieve normal conception and fertilization. It is already known that one-third of patients with active CD present a relapsing course during pregnancy, and, if conception occurs while the disease is active, a deterioration in two-thirds of the cases is observed^[2].

Likewise, UC is a chronic, inflammatory disease that predominantly occurs during reproductive age. Although controversial, studies indicate that UC may increase the risk for preterm births, suspension of full fetal development, and perinatal mortality. The controversy surrounding these studies arises from differences in their design and their usually small sample size^[3].

Two studies to date have reported an increased incidence of congenital abnormalities in fetuses of women with UC^[4-6]. Dominitz *et al*^[4] underscored that it is not possible to distinguish between small or large abnormalities and that chromosomal aberrations should also be taken into consideration. In another case series, it was reported that women with UC present with a 30% increase (though non-significant, 95%CI: 0.9-1.8) in congenital abnormalities of fetuses and a significantly higher risk of certain abnormalities, such as lesions in the extremities, obstruction of the urinary tract, and multiple genetic abnormalities.

Modern IBD treatment armamentarium includes biological therapy, such as anti-TNF agents, accompanied with concerns over their use during gestation. In

general, the Food and Drug Administration has categorized all drugs to five categories, A, B, C, D, and X, based on the incurring fetal risk. According to the Food and Drug Administration (FDA), category A consists of drugs for which controlled studies in women have failed to demonstrate a risk to the fetus in the first trimester, and, thus, fetal harm appears remote. Category B consists of either animal reproduction studies that have not demonstrated a fetal risk but have no corresponding human studies or animal studies that have shown adverse effects that have not been confirmed in controlled studies of women in the first trimester (or subsequent trimesters). Category C means that animal studies have revealed adverse fetal effects but that no controlled studies in women have been done or that no studies in women or animals are available. Category D consists of drugs for which human studies and/or adverse reaction data have shown evidence of fetal risk, but the benefits of use may outweigh the potential risks. Category X encompasses drugs in which human and animal studies have demonstrated fetal abnormalities, and the risk of using the drug in a pregnant woman clearly outweighs any benefit.

In particular, although there are limited data to date concerning the use of anti-TNF agents during pregnancy, no significant increases in the adverse outcomes of pregnancy have been reported in women who continued their treatment from conception to the first trimester of pregnancy^[7,8]. The FDA has classified these factors in category B. Most researchers, however, recommend discontinuing anti-TNF therapy prior to pregnancy^[7].

Decision making, however, in this case scenario dictates that the mother's benefits of maintaining relapse of the disease through continuation of anti-TNFs exceeds the potential risks of fetal exposure. The fact that antibodies transfer through the placenta at the end of the second and during the third trimesters suggests that the scheduled dosing of anti-TNF agents may continue in the first 20 wk of pregnancy and then should stop. However, Mishkin *et al*^[9] studied pregnancy outcomes in 92 to 122 cases and reported that the incidence of miscarriage and dead embryos was not significantly different than the general population and patients that are not under any biological treatment therapy.

Although biological drugs do not seem to possess any teratogenic properties, at least in animal models, they may inhibit maturation of the immunological system of the newborn child. Comparative studies between women with IBD exposed to anti-TNF agents during pregnancy and the general population did not demonstrate a high risk to the fetus incurred from anti-TNF use. It is important to note that there have been published cases of pregnant women who received anti-TNF drugs that did not report any side effects. Nevertheless, the FDA recommends that doctors

should evaluate each case with increased caution and prudence and not to encourage anti-TNF use during pregnancy unless necessary^[7].

With respect to IBD patients under biological treatment who become pregnant or if a pregnancy occurs while the disease is active, requiring immediate biological treatment, decisions should be made on an individual basis, as the short- and long-term effects of fetal exposure to these specific factors are still under investigation. Furthermore, there are as yet no clear guidelines regarding the best decision, which is a balance between the risks and benefits for the mother and the child, separately. Therefore, the decision whether or not to use biological treatment during pregnancy should be made carefully, especially because the levels of anti-TNF drugs in the maternal serum are unknown and it is uncertain whether this treatment is safe for the fetus^[10].

Adverse pregnancy outcomes, such as premature birth, miscarriages, preeclampsia, and low birth weight embryos, have been observed in certain cases of fetal exposure to biological agents. However, they tend to be balanced by the need for clinical remission of the pregnant woman, and also, they may be an outcome of the autoimmune disease itself. Information regarding birth defects caused by anti-TNF agents is scarce, and to our knowledge, only one study has reported on the incidence of birth abnormalities in the offspring of women who were under anti-TNF therapy at some stage during gestation^[11].

Therefore, there is a need for more clinical studies regarding the effect of anti-TNF therapeutic agents on pregnancy outcomes. The decision whether or not the agent compensates for the risk of fetal exposure should be taken carefully by the clinician (*e.g.*, gastroenterologist) in collaboration with the gynecologist. Finally, psychological support for the pregnant woman and scheduled monitoring throughout pregnancy are recommended.

ANTI-TNF AGENTS

Anti-TNF biological agents are either fully chimeric or humanized antibodies for ligands or soluble receptors, or recombinant receptor antagonists. Their mode of action concerns inhibition of TNF- α , based on the pleiotropic function of the molecule in cellular proliferation, cell adhesion, migration, and inflammatory cytokine induction response. Their main purpose, therefore, is interference on the inflammation pathway. However, the way they achieve this differs among monoclonal antibodies and soluble receptors^[12].

Monoclonal antibodies were the first molecules developed for the inhibition of TNF agents, and they are widely used today in clinical practice. The production of monoclonal antibodies from mice was originally developed for research purposes in the 1980s. Mouse monoclonal antibodies are derived from

cell lines, known as hybridomas^[13]. A few years after the production of monoclonal antibodies as therapeutic targets, soluble forms of the TNF receptor (TNF-R) were isolated from human urine. The unique form of soluble TNF-R was one subunit, but it was immediately abandoned because of reduced binding of the ligand. The design and production of the soluble dimeric TNF-R form was an important step for the development of biological therapies in medicine^[14].

As biological agents are protein molecules, they are quickly degraded inside the stomach. For this reason, they are parenterally administered, *i.e.*, either subcutaneously or intravenously at regular intervals^[15].

The administration of biological agents has been associated with a number of side effects that should be known to clinicians treating these patients. Selecting the correct patients to receive biological agents as well the constant and close monitoring of them are essential fundamentals for administering anti-TNF therapy safely^[16,17].

Currently, four anti-TNF agents, namely infliximab, adalimumab, certolizumab pegol, and golimumab, are FDA-approved for treatment of IBD.

SAFETY OF ANTI-TNF TREATMENT DURING PREGNANCY

Infliximab

It is currently unknown whether infliximab causes damage to the fetus when administered to the mother or even if it can affect the reproductive capacity of women. However, it is certain that it should be given to pregnant women only when necessary. Because it does not interact with TNF- α factor of other species besides humans and chimpanzees, there have been no reproductive studies conducted in laboratory animals using infliximab. No indication of maternal toxicity, embryotoxicity, or teratogenesis has been observed in any study conducted in mice, using a similar antibody, which has the ability to selectively inhibit the activity of murine TNF- α agent. As an immunoglobulin antibody, infliximab crosses the placenta and has been detected for more than 6 mo in neonatal serum from children born to mothers who received the treatment during pregnancy. Therefore, these newborns, may be at increased risk for infection, and their vaccinations should be carried out with special attention (FDA, 2015).

Multiple case reports refer to women with IBD who received infliximab during pregnancy, four of which were CD patients. The first described a 26-year-old CD patient who became pregnant while receiving infliximab infusions. She gave birth to a 681 g baby at 24 wk of gestation. The neonate developed internal bleeding and was disconnected from artificial support on the third day of birth and subsequently died. However, the severity of her disease and the fact that the patient conceived at the moment when

IBD was still active and that she was also under other medications could have affected the pregnancy outcome. In the remaining three pregnancies, two full-term and one premature, the newborns were still alive months after birth^[18,19].

More recently, the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) database has provided information for more patients. TREAT is a progressive record database, associated with studying patients with CD and evaluating safety of various treatments, including infliximab. These patients can be treated with infliximab or not. Of the 5807 patients who participated, there were 66 pregnancies, 36 of which were women under infliximab therapy prior to conception. Embryonic abnormalities were not observed in any of the embryos. Comparing patients who received infliximab vs those who did not, there were no significant differences in the rate of abortions (11.1% vs 7.1%, $P = 0.53$) and complications in newborns (8.3% vs 7.1%, $P = 0.78$). Patients under infliximab were more likely to exhibit severe form of the disease and to use steroids and immunomodulatory drugs^[20].

In 2004, Katz *et al.*^[20], elaborated a larger volume of information over the use of infliximab before and after gestation and published the first large-scale study on the probable outcome of pregnancy in women with CD. Data collection was based on drug indications, administration time in relation to conception, and course and outcome of pregnancy. The percentage of live embryos, miscarriages, and therapeutic abortions for women who were exposed to infliximab before or during gestation was comparable to the general population of pregnant women and to those of pregnant women with CD who had not received this specific therapy.

Of 146 identified pregnancies, 131 were exposed to infliximab, and data concerning their pregnancy outcome were provided for 96 cases. From these cases with known outcome, 64 (67%) resulted in live newborns, 14 (15%) in miscarriages, and 18 (19%) in termination for medical reasons. There were five reports of newborns born with complications: the first was born at 24 wk and expired, the second underwent a complex period of complications, the third was born with Fallot's tetralogy, the fourth developed an intestinal twist, and the last showed delayed growth and hypothyroidism. These results were similar to those of the general population of pregnant women and pregnant women with CD who did not receive infliximab. Based on these results, researchers concluded that the overall safety of the drug during gestation was not significantly different between women who received treatment and women who did not. However, an increased risk to the fetus was observed^[20].

The first study, concerning the intentional use of infliximab during pregnancy to induce and maintain remission of CD was conducted in 2005 by Mahadevan

et al.^[21]. All previous reports concerned unintentional or forced treatment for seriously ill women^[18-20]. This study included 10 women, eight of whom were receiving maintenance therapy with infliximab and one who had started drug administration at the third trimester of pregnancy due to a severe relapse of her CD. One of them started infliximab during the first trimester of pregnancy due to steroid-dependent disease but was not compliant and refused further treatment. Five pregnant women were also receiving mercaptopurine treatment, and another four were under corticosteroids, with the last one using steroids during the first trimester.

According to the results of the study^[21], four women exhibited no symptoms of the disease in the period from conception to labor (in the first two cases remission was observed and in the remaining two there was moderate disease activity). Two women showed disease improvement and four relapsed (two of them were in remission, although they relapsed after labor; the third showed mild relapse during the second trimester, but infliximab administration had just begun at that time; and the last developed a severe relapse and, therefore, started steroid administration). From those 10 women, eight gave birth by cesarean section (four due to active perianal disease, two due to active CD, one due to preterm birth, and the last due to a previous cesarean section). All 10 pregnancies resulted in live newborns. Congenital abnormalities were not observed in any of the fetuses, with an average follow up of 6 mo. Finally, there were three premature deliveries and two neonates with some embryonic disease not associated with infliximab. These data, in combination with earlier reports of accidental use of the drug during pregnancy, suggest that the benefit of infliximab use in inducing and maintaining remission in CD pregnant women usually outweighs fetal risk due to exposure to the agent^[21].

The most recent review^[22] concerning infliximab administration in IBD patients during gestation includes data until June 2014. It reported that infliximab crosses the placenta at the end of the second trimester of gestation. The use of the agent after the second trimester leads to intrauterine exposure. Although infliximab administration during gestation appears to be safe in the short term, there are concerns about the drug's effects on the development of the immune system of the fetus. Researchers argue that the administration of the drug should be discontinued, at least at the second trimester, when the mother is in remission, an approach considered safe for the mother that also minimizes the risk of fetal exposure to the agent. Infliximab has been detected in minor quantities in breast milk. Case reports do not suggest toxicity^[18,19], but the long-term effects of exposure are currently under investigation^[22].

Adalimumab

In 2002, the FDA has conducted an embryotoxicity

study^[23] of adalimumab in experimental animals and showed no harm incurring from this agent to the fetus for doses exceeding 100 mg/kg. However, in humans there are not sufficient data over its toxicity to the embryo. Since developmental and reproductive studies in laboratory animals are not always representative of the human response, it is reasonable to suggest that adalimumab should be administered during gestation only if considered necessary.

The first case report of maintenance treatment with adalimumab on IBD during pregnancy was conducted by Vesga *et al*^[24]. This report described the pregnancy course of a 34-year-old woman with chronic and active CD during conception. Infliximab administration was initially successful, but over time, the response was lost. Subsequently, adalimumab was introduced and continued until 1 mo before conception. During gestation, the patient received a total of 38 doses of 40 mg of the drug, subcutaneously. She continued the drug administration after labor and during breast-feeding.

In detail, the mother had active disease at the time of conception, mild symptomatic improvement in the first trimester of gestation, and mild disease activity during the third trimester. After labor, she showed mild to disease in remission. Pregnancy occurred without any complications, and the fetal prenatal ultrasound showed normal growth without visible congenital anomalies. Due to the history of perianal disease, a cesarean section was performed without complications at 38.5 wk. No neonatal abnormalities were detected. The newborn was monitored up to 6 mo and showed normal development and function^[24].

The next case report concerning the use of adalimumab during IBD pregnancy was published 1 year later by Mishkin *et al*^[9]. This particular case involved a 35-year-old female with persistent CD who did not respond to 5-aminosalicylic acid, antibiotics, or thiopurines. Seven years later, infliximab was introduced to the patient, initially with good clinical response. However, over time, she began requiring larger doses and smaller intervals between injections (every 4 or 6 wk), and she did not respond to the addition of corticosteroids. Adalimumab was then suggested at 80 mg initially and then 40 mg, subcutaneously, every second week. Her condition improved, but seven months after adalimumab initiation, she became pregnant.

By her own decision, she continued administration of the drug during gestation. She was admitted to a hospital at week 20 for unexplained fever and abdominal pain, but symptoms improved after a 2-wk course of steroids. She gave birth normally to a healthy neonate. Moreover, she continued treatment after labor and during breast-feeding. The newborn was monitored until 6 mo and showed normal development, in accordance to the previous study^[25].

Another case report described the pregnancy course of a 34-year-old woman with CD treated with

budesonide and then prednisone between weeks 6 and 20 of gestation. At this time, azathioprine was initiated at 100 mg/d, and adalimumab, initially, at 80 mg (one dose) and then at 40 mg every week. Labor was induced at 38 wk. The patient gave birth to a healthy newborn (2.89 kg) who developed normally until the age of 1 year^[25].

A subsequent case report described a 32-year-old woman with CD. Treatment with infliximab was successful in the first 17 mo of pregnancy. Then, her condition deteriorated, and she received adalimumab with an initial dose of 160 mg, followed by maintenance therapy, with a dose of 80 mg every other week. Remission was once again induced, and, therefore, medication was reduced to 40 mg every other week for further maintenance therapy, for a total of 18 doses. Overall, three non-intentional doses of adalimumab were given during the first trimester of gestation. At that time, treatment with adalimumab was automatically discontinued, and the patient and fetus were closely monitored for any side effects. Finally, the patient gave birth to a healthy newborn (3360 g), who remained healthy until the age of 2 years old^[26].

In a recent study by Schnitzler *et al*^[27], pregnancy outcome was recorded and risk-to-benefit ratio was assessed in 212 women with IBD under infliximab or adalimumab. Specifically, 42 pregnancies with direct exposure to anti-TNF agents (35 infliximab, seven adalimumab) were compared to 23 pregnancies before IBD diagnosis, 78 pregnancies before infliximab administration, 53 pregnancies with direct exposure to infliximab, and 56 pregnancies of healthy women.

The results of this study showed that 32 of the 42 pregnancies resulted in live fetuses, with an average gestational duration of 38 wk. Three resulted in premature birth, six were low weight newborns, and one had not been completed at that time. One of them (1640 kg) was born the 33rd week and died 13 d later due to necrotic colitis. A total of eight miscarriages was observed. A trisomy 18 was diagnosed in a mother with CD (aged 37 years) under adalimumab therapy, and the pregnancy was terminated. The outcomes of pregnancies with direct exposure to anti-TNF agents was not different from those that had discontinued therapy before pregnancy or from those with indirect exposure to the agent, but it was worse compared to pregnancies before IBD diagnosis^[27].

In a subsequent study by Zelinkova *et al*^[28], the focus was on the pregnancy of women with mild IBD who discontinued anti-TNF treatment. The investigators analyzed the levels of biological agents in omphalo-placenta samples. In total, 31 pregnancies were studied, with 28 of them exposed to anti-TNF agents (18 received infliximab and 13 adalimumab). Enzyme-dependent immunoprecipitation was used to measure the levels of factors in umbilical cord blood, collected from 18 newborns (12 of whom exposed to infliximab and six to adalimumab).

Among the patients who received infliximab, 12 (71%) discontinued treatment on the 30th week of gestation, and all patients remained in remission. All patients who received adalimumab discontinued treatment before 30th the week, which resulted in two relapses. Finally, 28 live newborns were born, there was one miscarriage in a patient receiving infliximab (on the 6th week of gestation), and two miscarriages among patients receiving adalimumab (on the sixth and eighth week). No congenital anomalies were observed^[28].

Certolizumab pegol and golimumab

Reproductive studies in laboratory animals are not possible to perform since certolizumab pegol is specific for humans. Likewise, golimumab effects on human pregnancies are lacking.

CONCLUSION

The decision to continue anti-TNF therapy during pregnancy is very difficult for both the clinician and the mother-patient. The aim is to maintain remission in the mother's disease while minimizing fetal exposure. It is a fact that placental transfer starts at the beginning of the second trimester of gestation and is maximized during the third. Therefore, it is preferable to avoid administering these agents in the third trimester of pregnancy. The decision should be made on an individual basis, always keeping in mind the distinct characteristics of the patient and her disease.

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